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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,496	06/09/2006	Dirk Finsinger	MERCK-3171	2879

23599 7590 08/06/2008

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
08/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,496	FINSINGER ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-9,13-15,19-28,30,31,33-35,37-42 and 47-51* is/are pending in the application.

4a) Of the above claim(s) *13,15,19-28,30,31,33-35 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-4, 8, 9, 14, 37-39, 47, 49, 51* is/are rejected.

7)☒ Claim(s) *3-7,40-42,47,49 -51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/EP04/12764 filed 11/11/2004 which claims priority to EP 03028268.5 filed 12/10/2003.

Claims 3-9, 13-15, 19-28, 30-31, 33-35, 37-42, 47-51 are pending. Claims 13, 15, 19-28, 30-31, 33-35, 48 are withdrawn from consideration. Claims 3-9, 14, 37-42, 47 49-51 are under examination.

Response to Arguments/Remarks

2. Applicant's representative's remarks and arguments in the reply filed on April 14, 2008 are acknowledged, however they fail to overcome all the rejections of record. The rejections of the canceled claims are withdrawn. The restriction requirement is apparently still being traversed and argued by counsel (Remarks at 108 and 109), who has suggested that the amended claims have met the unity of invention standard. This is not the case, since claim 34 clearly has non-novel alternatives, as shown previously. Regardless, the lack of unity was performed on the claims as presented originally (claims 1 & 2 etc.). The examiner does not determine unity of invention on claims that might be presented at a later date, but only those that were present at the time of action. The propriety of the restriction requirement will not be the subject of further discussion by the examiner, and should applicant wish to pursue this issue further the appropriate route is a petition under 37 C.F.R 1.144. The applicant has still not complied with the restriction requirement and it is unclear to the examiner which Q's are being used, since Q is apparently redefined numerous times. There is a Q in a phenyl ring and then another Q in the variable X, as shown below:

E, G, M, Q and U are each ~~independently~~ a carbon atom ~~selected from carbon atoms and nitrogen atoms, with the proviso that one or more of E, G, M, Q and U are carbon atoms and that X is bonded to a carbon atom~~,

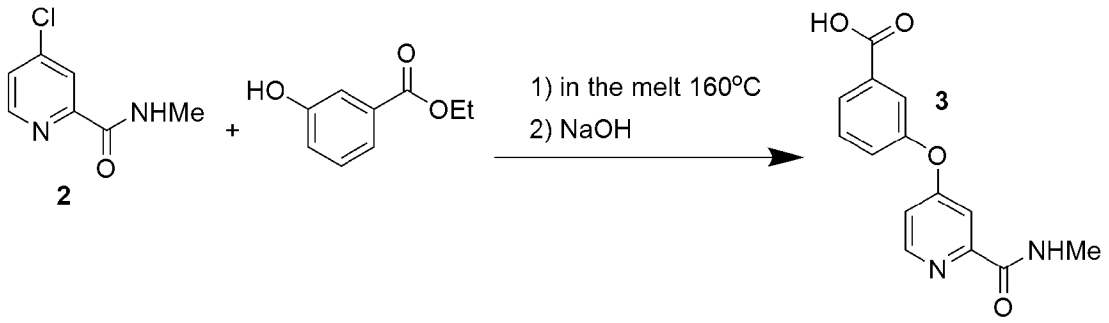
X is ~~represents~~ a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$,

Q is ~~selected from~~ T, $CH^{15}H^{16}$, $(CHal_2)_j$, $(O\text{-}CHR^{18})_j$, $(CHR^{18}\text{-}O)_j$, $CR^{18}=CR^{19}$, $(O\text{-}CHR^{18}CHR^{19})_j$, $CHR^{18}CHR^{19}\text{-}O)_j$, C=O, C=S, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, C(=O)O, OC(=O), OC(=O)O, C(=)$N(R^{15})$, $N(R^{15})C(=O)$, $OC(=O)N(R^{15})$, $N(R^{15})C(=O)O$, CH=N-O, $CH=N\text{-}NR^{15}$, $OC(O)NR^{15}$, $NR^{15}C(O)O$, S=O, SO_2, SO_2NR^{15}, or and $NR^{15}SO_2$,

While the numerous recitations of the second Q (the Q of X), do not correspond to the elected group and the redefining of the variable Q more than once could be appropriately rejected under 112 2nd paragraph, the examiner suggests that the first phenyl ring be redrawn as a phenyl ring thus eliminating the need for two Q's. In addition such an amendment would avoid any potential new matter rejections.

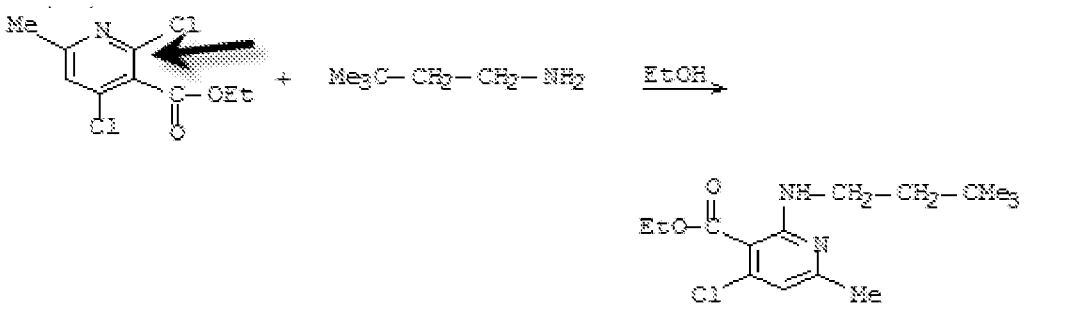
With respect to the enablement rejection, the rejection is maintained. The examiner would like to clarify some aspects of the rejection, as some of the points were apparently misunderstood. The examiner did not reject the claims for lack of enablement, but rather for the scope of enablement. The examiner was attempting to show, via sound referencing that the compounds claimed cannot be prepared without undue experimentation. In addition the rejection was made for the "how to use" requirement of 112 1st paragraph. The applicant has correctly pointed out (remarks pg. 112, line 3), that the examiner misidentified the halopyridine (compound **2**) as a bromopyridine, while it was actually a chloropyridine. In order to clarify and

make very clear as to what the examiner is referring to, a new Scheme 2 shown below has been constructed.



Scheme 2. Synthesis of compounds 3 of the instant case.

The reaction of phenols with halopyridines (compound **2**, pg. 158 and Scheme 1 created above) to yield the phenyl-pyridyl ethers (compound **3**, pg. 158 and Scheme 1 above) has several limitations as to what substituents are tolerated. The substituents on the phenol should be electron rich if it is *ortho* or *para* to the phenol oxygen, and the halopyridines should possess electron withdrawing groups (see March, J. *Advanced organic chemistry*, **1985**, 589). Contrary to the applicant's representative's assertion on page 112, that "nor does the rejection indicate why one skilled in the art would believe that this reaction does not proceed.", March states on the very first line of page 589, "that it generally requires activated substrates". In addition the applicant has argued that "As for substituents, the rejection also does not consider the use of protecting groups or the introduction of substituents after the formation of a phenyl-pyridyl ether structure." Protecting groups are routinely used for reactive oxygen and nitrogen groups, but many groups cannot be protected, apparently the chemist of ordinary skill can design new protecting groups at will. Of course this is not the case and research into new protecting groups is actually a field of research. Exactly how does one protect a halogen atom? Consider the following known reaction from the literature, which shows that a 2-halo pyridine is more reactive towards nucleophilic substitution (Fitch WO 2007103905 abstract only).



NOTE: microwave irradiation
CON: STAGE(1) room temperature -> 150 deg C; 0.5 hours, 150 deg C

It was argued repeatedly that "the introduction of substituents after the formation of a phenyl-pyridyl ether structure" could be done, however no guidance as to what these substituents are or how they are installed is given. With respect to the reaction of olefins and alkynes with phenols, this is a well known reaction and supported by ample citations. The suggestion (remarks at 112), that an intermolecular reaction between the phenol and chloropyridine would proceed faster than an intramolecular reaction between a phenol bearing a pendant alkylhalide or olefin or alkyne is highly suspect. Such a suggestion goes against the most basic scientific reasoning and a citation of this well-known fact hardly seems necessary.

It is clear that chemistry always presents unforeseen problems and that it is inherently an experimental science. However in the eyes of the unskilled, these considerations do not occur at all. The examiner is attempting to establish the facts as to the state of the art, while the applicant's representative is simply making vague statements as to why the claims are operable.

Notwithstanding the how to make aspect it is well known that molecular structure is correlated with physical properties. The medicinal chemistry of kinase inhibitors is relatively well-developed and many limitations are well known in the art. No trail is blazed to support the instantly claimed genus or guide the skilled artisan to some particular area where experimentation might take place. It is neither obvious nor predictable, to make such modifications.

In this case the claims bear no structural resemblance to the exemplified compounds, which are relatively homogenous and non-representative of the scope claimed. In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. The specification

gives literally no guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. Only a few compounds were made, with respect to different substituent groups. In fact the only variation appears on R^8, and it is a modest variation alkyl, O-alkyl-NH_2, CF_3, halogen, O-alkyl, and S-alkyl, OCF_3, everything else is constant. See *Ex parte Herzog, Hershberg, and Coan*, 115 USPQ 195 (Bd. Pat. App. & Int. 1956) affirming the examiner, and stating "it becomes obvious that the expressions defining the organic acids used.....are inclusive of inoperative materials and go far beyond the adequately disclosed subject matter of the specification." And also *Ex parte DIAMOND,* 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

"the specification contains 23 specific examples, but it will be noted that they are to the preparation of relatively simple compounds.....This must be regarded as a relatively meagre and nonrepresentative disclosure to support claims which embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57 ; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637. In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court held that 'An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class.'"

In addition *In re Fouche* 169 USPQ 429 dealt with a similar issue with respect to how to use requirement of 112 1st paragraph,

"Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art. It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a

Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group."

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)

"Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected."

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Prutton, 96 USPQ 147 (C.C.P.A. 1952)

"The complete list of organic compositions includes, in generic form, most of the organic compounds found discussed in ordinary textbooks of organic chemistry..... It appears to be appellant's view that a selection of an unsaturated hydrocarbon from the first list and of a sulphide of phosphorus from the second list will provide support for the claims here under discussion. The Examiner holds, and properly we think, that the presentation of such lists from which reagents may be selected is not a sufficient disclosure to support claims to a particular class of reaction product which might be produced by proper selection of reagents and determining the conditions of reaction."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the

chemicals or chemical combinations included therein were generally capable of accomplishing the desired result." See *In re Ellis*, 37 App. D. C. 203; *In re Dosselman*, 37 App. D. C. 211; *In re Langmuir*, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

In Re Sus and Schaefer 134 USPQ 1962 301-310 (*affirmed*):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the *invention claimed* shall be no broader than the *invention set forth* in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only *certain aryl radicals* and certain specifically substituted aryl radicals would be suitable for such purposes." Emphasis in Original.

The examiner has more than made his case for the enablement rejection. The rejection for solvate is maintained, although the examiner takes the applicant's point and appreciates the citations, since no working examples are found unfortunately the examiner must maintain the rejection. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 3-4, 8, 14, 37-39, 47, 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows:

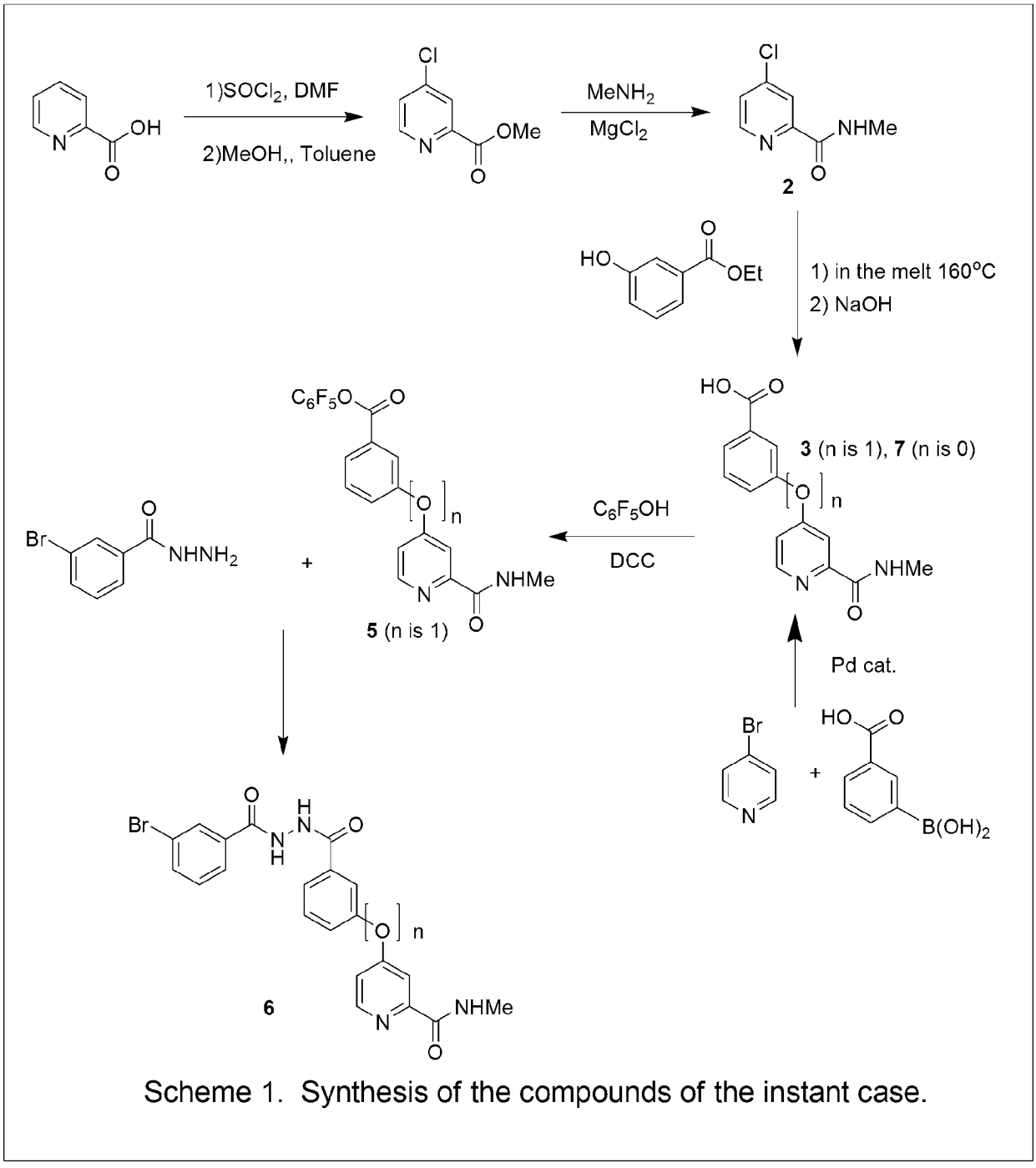
The variables in claim 6, with a definition of R^9 as H. In addition enablement on R^8 has been provided for alkyl, O-alkyl-NH_2, CF_3, halogen, O-alkyl, and S-alkyl, OCF_3 .

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all known chemical structures and heretofore unknown groups defined only by number atoms, the size of a ring (claim 1), and other groups bearing multiple substitutions of undefined structure "a carbon based moiety" **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity as a raf kinase inhibitor. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (**C**, **E-H**) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the chemistry required to prepare the compounds. The only example given is that of pgs. 157-161, reproduced in Scheme 1.



Scheme 1. Synthesis of the compounds of the instant case.

The chemistry used to construct the compounds is not applicable to the scope claimed and currently no methods exist for the scope claimed. The limitations of synthetic chemistry are readily apparent as stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface]…….even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]…….. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]…….. As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8]……...Even the most experienced chemist will not be able

> to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. **(E)**

The reaction of phenols with halopyridines (compound **2**, pg. 158 and Scheme 1 created above) to yield the phenyl-pyridyl ethers (compound **3**, pg. 158 and Scheme 1 above) has several limitations as to what substituents are tolerated. The substituents on the phenol should be electron rich if it is *ortho* or *para* to the phenol oxygen, and the halopyridines should possess electron withdrawing groups (see March, J. *Advanced organic chemistry*, **1985**, 589). It is somewhat surprising that other halogens are claimed, as the other halogens are well known to react in such reactions (see March, J. *Advanced organic chemistry*, **1985**, 589). The most disturbing examples in the instant case are listed as alkylhalide on R8, which will give cyclic ethers via the well known Williamson ether synthesis March pg. 342-343. In addition alkynes and alkenes will undergo addition of phenol as is well known (March *Advanced organic chemistry* pg. 684-685.) If this alkyne is terminal it will be deprotonated and undergo subsequent reaction with other electrophilic groups. Intramolecular cyclization of the phenol oxygen onto pendant olefins and alkynes in the ortho position as is well known in the art. Hurd et. al. *J. Am. Chem. Soc.* **1940**,*5*, 212-222, entire document) teach that olefins react to give chromans (applicant heats the reaction to 160°C in subsequent steps). Buckle et. al *J. Chem. Soc.*

Perkin Trans. 1 **1985**, 2443-2446 entire document, teaches that phenolate anions with pendant alkynes will produce benzofurans.

The synthesis of the pyridyl-phenyl moiety via the Suzuki-coupling is likewise limited (i.e. the synthesis of compound **7**, pg. 161 and Scheme 1 above). It is well known in the art that Pd undergoes oxidative addition to "halo" a substituent (readily to I, and Br), which is recited for numerous variables. The applicant's own disclosure is shown as evidence of this fact. One reviewer has made the following statement about Pd-cataylzed cross-couplings:

> The large number of highly diverse examples of high-yielding Pd-catalyzed organic reactions might give the non-specialist the impression that almost any conceivable transformation might work in the presence of a suitable Pd catalyst. This is, of course, not true, and even the most robust Pd-catalyzed processes have their limitations. Some of these will be discussed in the following sections. The most important unwanted processes which can compete with Pd(0)-catalyzed C-C bond formation include homocoupling or reduction of the halide and homocoupling, C-protonation, or oxidation of the organometallic reagent. (Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim Chapter 8, pgs. 279-308.)

Dorwald has numerous references to reactions that do not work. In particular in the instant case the claims are directed to groups of the instant case that will result in undesired processes that do not lead to the product. When a substituent is alkyl and ortho to bromo, a variety of cylcometallation process can occur and "give rise to unexpected products or, if the palladacycles are too stable, the catalyst will be consumed and no further reaction will occur." (Dorwald ibid. pgs. 298-299). In addition certain ortho groups will chelate the metal and prevent reaction: "Accordingly, aryl halides with strongly chelating ortho-substituents will undergo transition metal-catalyzed C-C bond formation only sluggishly or not at all." (Dorwald ibid. 300-301). It is also a well known limitation of Pd catalyzed reactions that sterically bulky substituents hinder or completely inhibit the reaction.

Many of the compounds currently under the Markush claim could not exist but would self-polymerize instantaneously if prepared as stated by Dorwald ibid. pg. 41 "It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly…" **(C & E)**

See I*n re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how compounds with these vast substituents are to be obtained. Where may the directions to prepare or buy them be found? **(F)**

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula).

While these chemical limitations are significant, even more significant are the limitations of activity at raf kinase. What are the important structural features for the claimed utility? **(**The medicinal chemistry of raf kinase inhibitors is relatively well-developed and many limitations are well known in the art. It is sensitive to structural changes that may be relatively minor in the chemical sense see Timothy B. Lowinger, Bernd Riedl, Jacques Dumas and Roger A. Smith "Design and Discovery of Small Molecules Targeting Raf-1 Kinase" *Current Pharmaceutical Design*, 2002, 8, 2269-2278 2269,

"Initial medicinal chemistry efforts indicated that variation of substituents on the phenyl group in **4** had the potential to provide significant optimization of inhibitor potency (Table 1) [21, 22]. At the *para* position, small lipophilic substituents such as methyl and chloro provided an increase in potency (**5**, **6**); however**, a size limitation was revealed, as this improvement was lost with substituents having greater steric bulk** (e.g., **11–13**)…… Structure–activity trends were similar to those observed in the phenyl series, as the best analogs in this sub-class were substituted with small lipophilic groups (i.e., 30–32)." Pg. 2270

Indeed it is clear that if a substituent that is too large, or not lipophillic enough, this leads to compounds with no activity. Compound **87** which differs from compound **77** only by the substitution of phenyl for isopropyl was devoid of activity. The relevant portion of Table 3 from Lowinger et. al. is reproduced below for convenience.

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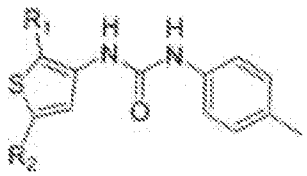
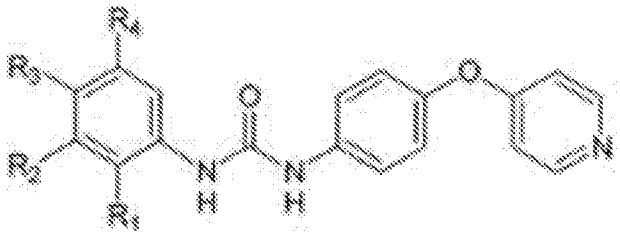
Table 3. Replacements for the Thiophene Substituents in 5



Compounds	R_1	R_2	Raf-1 kinase % inh. (25 μM)	Raf-1 kinase IC_{50} (μM)
77	$COOCH_3$	iPr		4.0
87	$COOCH_3$	Ph	0	

Moving closer to the compounds of the instant case bearing a pyridyloxy linkage to the phenyl group as in Table 11 of Lowinger et. al. While only limited information regarding a relatively small group of lipophillic substituents is available, minor changes result in markedly different activity (see the movement of the position of a chlorine atom **155** vs. **158**).

Table 11. SAR of Diphenyl Ureas Derived from the 4-(4-pyridyl-oxy)Aniline Side-chain



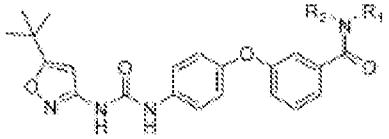
Compound	R_1	R_2	R_3	R_4	Raf-1 IC_{50} (nM)
155	H	H	Cl	CF_3	46
156	H	CF_3	H	CF_3	600
157	OCH_3	Cl	H	H	2,700
158	Cl	H	H	CF_3	450
159	H	H	H	CF_3	460
160	OCH_3	H	NO_2	H	4,400
161	F	H	H	CF_3	720
162	H	OCH_3	H	CF_3	510
163	H	H	H	OCF_3	440
164	H	H	Br	CF_3	35
165	H	H	F	CF_3	530
166	H	H	Cl	Br	450
167	OCH_3	H	Cl	CF_3	29

Moreover compound 119 of Lowinger et. al. is devoid of activity, yet the chemical change is relatively modest:

"The urea moiety clearly appeared essential for kinase inhibitory activity. Both *N*-Me derivatives **116** and **117**, as well as the cyclic urea derivative **118**, showed a dramatic loss of activity. Similarly, exchange of one nitrogen atom for a carbon as in amide **119** also resulted in a completely inactive compound."

It is apparent that caroboxamides are a preferred substituent, however it is far from clear what the effects of substitution on the carboxamide moiety is. Indeed secondary amides seem to be disfavored, based on the prior art teaching of Uday R. Khire et. al. "Omega-carboxypyridyl substituted ureas as Raf kinase inhibitors: SAR of the amide substituent." *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 783–786. A relatively minor change of H to methyl results in a 50 fold decrease in activity, see Table 1 compound **2** vs. compound **8**, (R1). Table 1 of Khire is shown below:

Table 1. Substitution of the carboxamide group



Compd	R_1	R_2	Raf-1 kinase IC_{50} (nM)[a]
2	H	Me	120
6	H	Et	130
7	H	*n*-Pr	140
8	Me	Me	5800
9	H	CH_2Ph	460
10	H	Ph	370
11	H	3-Pyridyl	68

It is clear that substituents are chosen rationally based on scientific reasoning not capriciously, see the footnote on pg. 2778, ref. 12.

"12 "Building blocks were selected 'manually' with the objective of achieving a balance of structural diversity and similarity to the hit **2**. These building blocks included a total of 75

isocyanates and ca. 300 amines, including some custom-prepared compounds. About 1500 syntheses were attempted, and ca. 1000 products were obtained having purities of >60% (HPLC, 254 nm) and confirmed identities (LC/MS).[10a] These 1000 products were submitted for testing, and keyactives that were identified were resynthesized, purified, characterized, and re-tested."

In the instant case, the amount of information provided with respect to which substituents are required for activity is noticeably absent. In fact the specification is devoid of any data regarding the activity of the compounds. **(F & G)** In this case these compounds bear a remarkable structural resemblance to one another, yet the claims are not commensurate in scope. Based on the state of the prior art, the claims of the instant case are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only very few working examples in this unpredictable art without undue experimentation. **(C, E, F, G, H).**

6. Claims 1-4, 9, 49, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of

working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims. g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. h) The breadth of the claims includes all of the hundreds of thousands of compounds

of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Objections

7. Claims 5-7, 40-42, 47, 49, 50 are objected to for depending from a rejected base claim.

8. Claims 3-4, & 49 are objected to for being drawn to a non-elected invention. A reply to this FINAL rejection must include a cancellation of non-elected subject matter.

9. Claims 51 is objected to for being a duplicate of claim 3.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000..

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625